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# Topiramate for neuropathic pain and fibromyalgia in adults (Review)

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*Cochrane Database of Systematic Reviews* 2013, Issue 8. Art. No.: CD008314.
DOI: 10.1002/14651858.CD008314.pub3.

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[Intervention Review]

# Topiramate for neuropathic pain and fibromyalgia in adults

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**Editorial group:** Cochrane Neuromuscular Group.
**Publication status and date:** Stable (no update expected for reasons given in 'What's new'), published in Issue 7, 2016.

**Citation:** Wiffen PJ, Derry S, Lunn MPT, Moore RA. Topiramate for neuropathic pain and fibromyalgia in adults. *Cochrane Database of Systematic Reviews* 2013, Issue 8. Art. No.: CD008314. DOI: 10.1002/14651858.CD008314.pub3.



## ABSTRACT

### Background

Topiramate is an antiepileptic drug with multiple possible mechanisms of action. Antiepileptic drugs are widely used to treat chronic neuropathic pain (pain due to nerve damage) and fibromyalgia, and many guidelines recommend them.

### Objectives

To assess the analgesic efficacy and associated adverse events of topiramate for chronic neuropathic pain and fibromyalgia in adults (aged 18 years and above).

### Search methods

On 8 May 2013, we searched the Cochrane Neuromuscular Disease Group Specialized Register, CENTRAL, MEDLINE, and EMBASE. We reviewed the bibliographies of all randomised trials identified and review articles, and also searched two clinical trial databases, ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform, to identify additional published or unpublished data.

### Selection criteria

We included randomised controlled trials (RCTs) with double-blind assessment of participant outcomes following two weeks of treatment or longer (though the emphasis of the review was on studies of eight weeks or longer) that used a placebo or active comparator.

### Data collection and analysis

We extracted efficacy and adverse event data, and two study authors examined issues of study quality independently. We performed analysis using two tiers of evidence. The first tier used data where studies reported the outcome of at least 50% pain reduction from baseline, lasted at least eight weeks, had a parallel group design, included 200 or more participants in the comparison, and reported an intention-to-treat analysis. First tier studies did not use last-observation-carried-forward (LOCF) or other imputation methods for dropouts. The second tier used data that failed to meet this standard; second tier results were therefore subject to potential bias.

### Main results

We included four studies with 1684 participants. Three parallel-group placebo comparisons were in painful diabetic neuropathy (1643 participants), and one cross-over study with diphenhydramine as an active placebo (41 participants) was in lumbar radiculopathy. Doses of topiramate were titrated up to 200 mg/day or 400 mg/day. All studies had one or more sources of potential major bias, as they either used LOCF imputation or were of small size.

No study provided first tier evidence for an efficacy outcome. There was no convincing evidence for efficacy of topiramate at 200 to 400 mg/day over placebo.

Eighty-two per cent of participants taking topiramate 200 to 400 mg/day experienced at least one adverse event, as did 71% with placebo, and the number needed to treat for an additional harmful effect (NNTH) was 8.6 (95% confidence interval (CI) 4.9 to 35). There was no difference in serious adverse events recorded (6.6% versus 7.5%). Adverse event withdrawals with 400 mg daily were much more common with topiramate (27%) than with placebo (8%), with an NNTH of 5.4 (95% CI 4.3 to 7.1). Lack of efficacy withdrawal was less frequent with topiramate (12%) than placebo (18%). Weight loss was a common event in most studies. No deaths attributable to treatment were reported.

**Authors' conclusions**

Topiramate is without evidence of efficacy in diabetic neuropathic pain, the only neuropathic condition in which it has been adequately tested. The data we have includes the likelihood of major bias due to LOCF imputation, where adverse event withdrawals are much higher with active treatment than placebo control. Despite the strong potential for bias, no difference in efficacy between topiramate and placebo was apparent.

## PLAIN LANGUAGE SUMMARY

**Topiramate for treating neuropathic pain or fibromyalgia**

Neuropathic pain is pain coming from damaged nerves. It is different from pain messages carried along healthy nerves from damaged tissue (for example from a fall, a cut, or arthritic knee). Neuropathic pain is treated by different medicines than pain from damaged tissue. Medicines like paracetamol or ibuprofen are not effective in treating neuropathic pain, while medicines that are sometimes used to treat depression or epilepsy can be very effective in some people with neuropathic pain. Our knowledge about fibromyalgia is even less advanced, but fibromyalgia can respond to the same medicines as neuropathic pain.

Topiramate is a medicine used to treat epilepsy, and so it might be a useful medicine for neuropathic pain or fibromyalgia.

On 8 May 2013, we performed searches to look for clinical trials on the use of topiramate to treat neuropathic pain or fibromyalgia. We found four studies of reasonable quality that tested topiramate against placebo for a number of weeks. Almost all of the 1684 people in the studies had painful limbs because of damaged nerves caused by diabetes.

Topiramate did not help the pain and was no different from placebo except in causing more side-effects, which made many more people withdraw from the studies early. About 3 people in 10 withdrew because of side-effects with topiramate compared with 1 in 10 with placebo.

Topiramate has not been shown to work as a pain medicine in diabetic neuropathy.

**Summary of findings for the main comparison. Topiramate 200 to 400 mg versus placebo for neuropathic pain**

**Intervention: topiramate 200 to 400 mg compared with placebo**

**Patient or population: neuropathic pain (two studies found in painful diabetic neuropathy, and one in lumbar radiculopathy)**

**Settings: community**

**Intervention: oral topiramate 200 to 400 mg daily**

**Comparison: oral placebo**

| Outcome | Probable outcome with intervention | Probable outcome with comparator | NNTB or NNTH and/or relative effect (95% CI) | Number of participants | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| At least 50% reduction in pain or equivalent | No adequate data | No adequate data | No adequate data | 317 participants<br>(1 study) | | Diabetic peripheral neuropathy<br>LOCF imputation makes any estimate an overestimation, and bulk of data in studies report no difference between topiramate and placebo Low numbers |
| "Moderate" benefit<br>At least 30% reduction in pain | No adequate data | No adequate data | No adequate data | 317 participants<br>(1 study) | | Diabetic peripheral neuropathy<br>LOCF imputation makes any estimate an overestimation, and bulk of data in studies report no difference between topiramate and placebo Low numbers |
| Proportion below 30/100 mm on VAS | No data | | | | | |
| Patient Global Impression of Change much or very much improved | No adequate data | No adequate data | No adequate data | 399 participants<br>(2 studies) | | Variously reported, and inadequate numbers for satisfactory analysis |
| Adverse event withdrawals | 270 in 1000 | 81 in 1000 | NNTH 5.4 (4.3 to 7.1)<br>RR 3.4 (2.4 to 4.7) | 1038 participants<br>178 events | Moderate quality | Low number of events |

| | | | | | | |
|---|---|---|---|---|---|---|
| Serious adverse events | 66 in 1000 | 75 in 1000 | NNTH not calculated<br><br>RR 0.9 (0.6 to 1.3) | 1586 participants<br><br>110 events | Moderate quality | Low number of events |
| Death | There were no deaths related to treatment | | | | | |

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

LOCF: last observation carried forward; VAS: visual analogue scale; NNTB: number needed to treat for an additional beneficial effect: NNTH: number needed to treat for an additional harmful effect; RR: risk ratio.

# BACKGROUND

## Description of the condition

The 2011 International Association for the Study of Pain definition of neuropathic pain is "pain caused by a lesion or disease of the somatosensory system" (Jensen 2011), based on an earlier consensus meeting (Treede 2008). Neuropathic pain may be caused by nerve damage, but it is often followed by changes in the central nervous system (CNS) (Moisset 2007). It is complex (Apkarian 2011; Tracey 2011), and neuropathic pain features can be found in patients with joint pain (Soni 2013). Moreover, patients with neuropathic pain and fibromyalgia experience similar sensory phenomena (Koroschetz 2011).

Neuropathic pain tends to be chronic and may be present for months or years. Fibromyalgia is defined as widespread pain for longer than three months with pain on palpation at 11 or more of 18 specified tender points (Wolfe 1990), and it is frequently associated with other symptoms, such as poor sleep, fatigue, and depression. More recently, a definition of fibromyalgia has been proposed based on symptom severity and the presence of widespread pain (Wolfe 2010). The cause, or causes, are not well understood, but it has features in common with neuropathic pain, including changes in the CNS. Many people with these conditions are significantly disabled with moderate or severe pain for many years.

In primary care in the UK the incidences, per 100,000 person years observation, have been reported as 28 (95% CI 27 to 30) for postherpetic neuralgia, 27 (95% CI 26 to 29) for trigeminal neuralgia, 0.8 (95% CI 0.6 to 1.1) for phantom limb pain, and 21 (95% CI 20 to 22) for painful diabetic neuropathy (Hall 2008). Estimates vary between studies, often because of small numbers of cases. The incidence of trigeminal neuralgia has been estimated at 4 in 100,000 per year (Katusic 1991; Rappaport 1994), while more recently, a study of facial pain in The Netherlands found incidences per 100,000 person years of 12.6 for trigeminal neuralgia and 3.9 for postherpetic neuralgia (Koopman 2009). A systematic review of chronic pain demonstrated that some neuropathic pain conditions, such as painful diabetic neuropathy, can be more common, with prevalence rates up to 400 per 100,000 person years (McQuay 2007) illustrating how common the condition was as well as its chronicity. The prevalence of neuropathic pain was reported as being 3.3% in Austria (Gustorff 2008), 6.9% in France (Bouhassira 2008), as high as 8% in the UK (Torrance 2006), and about 7% in a systematic review of studies published since 2000 (Moore 2014). Some forms of neuropathic pain, such as diabetic neuropathy and postsurgical chronic pain (which is often neuropathic in origin) are increasing (Hall 2008). Fibromyalgia is common, especially in women, with an all-age prevalence of 12% and a female to male ratio of 6:1 (McNally 2006).

Neuropathic pain and fibromyalgia are known to be difficult to treat effectively, with only a minority of individuals experiencing a clinically relevant benefit from any one intervention. A multidisciplinary approach is now advocated, with pharmacological interventions being combined with physical or cognitive interventions, or both. Conventional analgesics are usually not effective. Some patients may derive some benefit from a topical lidocaine patch or low concentration topical capsaicin, though evidence about benefits is uncertain (Derry 2012; Khaliq 2007). High concentration topical lidocaine may benefit some patients with postherpetic neuralgia (Derry 2013). Treatment is more usually by so-called unconventional analgesics such as antidepressants like duloxetine and amitriptyline (Lunn 2009; Moore 2012a; Sultan 2008) or antiepileptics like gabapentin or pregabalin (Moore 2009; Moore 2011). An overview of treatment guidelines points out some general similarities, but also differences in approach (O'Connor 2009). The proportion of patients who achieve worthwhile pain relief (typically at least 50% pain intensity reduction (Moore 2013)) is small, generally 10% to 25% more than with placebo, with the number needed to treat for an additional beneficial outcome (NNTB) usually between 4 and 10.

Chronic painful conditions comprised five of the 11 top-ranking conditions for years lived with disability in 2010 (Vos 2012), and are responsible for considerable loss of quality of life and employment, and increased health costs (Moore 2014).

## Description of the intervention

Topiramate is a weak inhibitor of carbonic anhydrase isoenzymes (Kanda 1996). Therefore, it is associated with carbonic anhydrase-related adverse effects such as nephrolithiasis, metabolic acidosis and potentially a compensatory hyperventilating respiratory alkalosis, and perioral or digital paraesthesias. Other well-recognised adverse effects of topiramate include somnolence (sleepiness), dizziness, fatigue, nausea, poor concentration, and weight loss (Chong 2003; Walia 2004). Topiramate is associated with weight loss (Antel 2012), and there are reports of reversible anorgasmia in men and women (Sun 2006). Topiramate does not appear to be associated with oral cleft or major congenital malformations in the newborn when taken by women during pregnancy (Green 2012).

Topiramate is licensed for the treatment of epilepsy and as a prophylaxis for migraine in the UK and USA. These indications have been the subjects of separate Cochrane reviews (Chronicle 2004; Jette 2008). Topiramate is taken orally and is available as 25 mg, 50 mg, 100 mg, and 200 mg tablets, and 15 mg, 25 mg, and 50 mg sprinkle capsules. It is marketed under the trade name Topamax®, and generic formulations are available. The dose is usually titrated slowly, to minimise adverse effects, until a therapeutic response is achieved, or tolerability reached.

## How the intervention might work

Topiramate has multiple modes of action, some of which are thought to be useful in the treatment of neuropathic pain. Topiramate has been shown to block activity-dependent, voltage-gated sodium channels, enhance the action of ɣ-aminobutyric acid (GABA)-A receptors, inhibit L-type voltage-gated calcium channels, pre-synaptically reduce glutamate release, and post-synaptically block kainate/α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (Chong 2003), all of which have been reported to be involved in the genesis or control of neuropathic pain.

## Why it is important to do this review

Topiramate has been used to treat various neuropathic pain conditions, using various study designs, with conflicting results. It is important to review all the evidence to determine its place in the treatment of neuropathic pain and fibromyalgia.

The original review of antiepileptic drugs for neuropathic pain has been withdrawn (Wiffen 2010, originally published in 2005) and

split into reviews for individual drugs, including carbamazepine (Wiffen 2011a), lamotrigine (Wiffen 2011b), gabapentin (Moore 2011), pregabalin (Moore 2009), valproic acid (Gill 2011), phenytoin (Birse 2012), and clonazepam (Corrigan 2012). These separate reviews for individual drugs use more stringent criteria of validity, which include the level of response obtained, the duration of study, and method of imputation of missing data (Moore 2012a). Appendix 1 gives details of recent changes to the thinking about chronic pain and evidence.

This Cochrane review therefore assesses evidence in ways that make both statistical and clinical sense, and uses developing criteria for what constitutes reliable evidence in chronic pain (Moore 2010a). Studies included and analysed have to meet minimum criteria for reporting quality (blinding, randomisation), validity (duration, dose and timing, diagnosis, outcomes, etc), and size (ideally at least 200 participants in each treatment arm in a comparison in which the number needed to treat for an additional beneficial outcome (NNTB) is four or above (Moore 1998)). This does set high standards and marks a departure from how reviews have been done previously.

This review will be one of a series to be included in an overview of antiepileptic drugs for neuropathic pain and fibromyalgia.

## OBJECTIVES

1. To assess the analgesic efficacy of topiramate for chronic neuropathic pain and fibromyalgia in adults (aged 18 years and above).
2. To assess the adverse events associated with the clinical use of topiramate for chronic neuropathic pain and fibromyalgia in adults.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We included studies if they were randomised controlled trials (RCTs) with double-blind assessment of participant outcomes following two weeks of treatment or longer, though the emphasis of the review was on studies of eight weeks or longer. We required full journal publication, with the exception of online clinical trial results summaries of otherwise unpublished clinical trials and abstracts with sufficient data for analysis. We did not include short abstracts (usually meeting reports). We excluded studies that were non-randomised, studies of experimental pain, case reports, and clinical observations.

#### Types of participants

Studies included adult participants aged 18 years and above. Participants could have one or more of a wide range of chronic neuropathic pain conditions, including:

- painful diabetic neuropathy;
- postherpetic neuralgia;
- trigeminal neuralgia;
- phantom limb pain;
- postoperative or traumatic neuropathic pain;
- complex regional pain syndrome;
- cancer-related neuropathy;
- human immunodeficiency virus (HIV) neuropathy;
- spinal cord injury;

or

- fibromyalgia;
- complex regional pain syndrome (CRPS) Type I.

If studies included participants with more than one type of neuropathic pain we planned to analyse results according to the primary condition.

We excluded migraine and headache studies as they are the subject of another Cochrane review (Chronicle 2004).

#### Types of interventions

Oral topiramate, at any dose, administered for the relief of neuropathic pain or fibromyalgia and compared to placebo or any active comparator.

#### Types of outcome measures

We anticipated that studies would use a variety of outcome measures, with the majority of studies using standard subjective scales (numerical rating scale (NRS) or visual analogue scale (VAS)) for pain intensity, pain relief, or both. We were particularly interested in Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) definitions for moderate and substantial benefit in chronic pain studies (Dworkin 2008). These are defined as at least 30% pain relief over baseline (moderate), at least 50% pain relief over baseline (substantial), much or very much improved on Patient Global Impression of Change (PGIC) (moderate), and very much improved on PGIC (substantial). These outcomes are different from those set out in the earlier review (Wiffen 2010), concentrating as they do on dichotomous outcomes where pain responses do not follow a normal (Gaussian) distribution. People with chronic pain desire high levels of pain relief, ideally more than 50%, and with pain not worse than mild (O'Brien 2010).

We included a 'Summary of findings' table as set out in the Cochrane Pain, Palliative and Supportive Care Group author guide (PaPaS 2011). The 'Summary of findings' table includes outcomes of at least 30% and at least 50% pain intensity reduction, PGIC, adverse event withdrawals, serious adverse events, and death.

##### *Primary outcomes*

1. Patient-reported pain relief of 30% or greater.
2. Patient-reported pain relief of 50% or greater.
3. PGIC much or very much improved.
4. PGIC very much improved.

##### *Secondary outcomes*

1. Any pain-related outcome indicating some improvement.
2. Withdrawals due to lack of efficacy.
3. Participants experiencing any adverse event.
4. Participants experiencing any serious adverse event. Serious adverse events typically include any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing

hospitalisation, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, is an 'important medical event' that may jeopardise the patient, or may require an intervention to prevent one of the above characteristics or consequences.

5. Withdrawals due to adverse events.
6. Specific adverse events, particularly somnolence and dizziness.
7. Weight loss or weight change.

These outcomes were not eligibility criteria for this review, but were outcomes of interest within included studies.

## Search methods for identification of studies

### Electronic searches

The following databases were searched:

- the Cochrane Neuromuscular Disease Group Specialized Register (8 May 12013);
- the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* (Issue 4, 2013);
- MEDLINE (January 1966 to April 2013); and
- EMBASE (January 1980 to April 2013).

The detailed search strategies are in the appendices: Appendix 2 (MEDLINE), Appendix 3 (EMBASE), and Appendix 4 (CENTRAL).

### Searching other resources

We reviewed the bibliographies of all randomised trials identified and review articles and searched two clinical trial databases (ClinicalTrials.gov (ClinicalTrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTTRP) (http://apps.who.int/trialsearch/)) to identify additional published or unpublished data. We did not contact investigators or study sponsors.

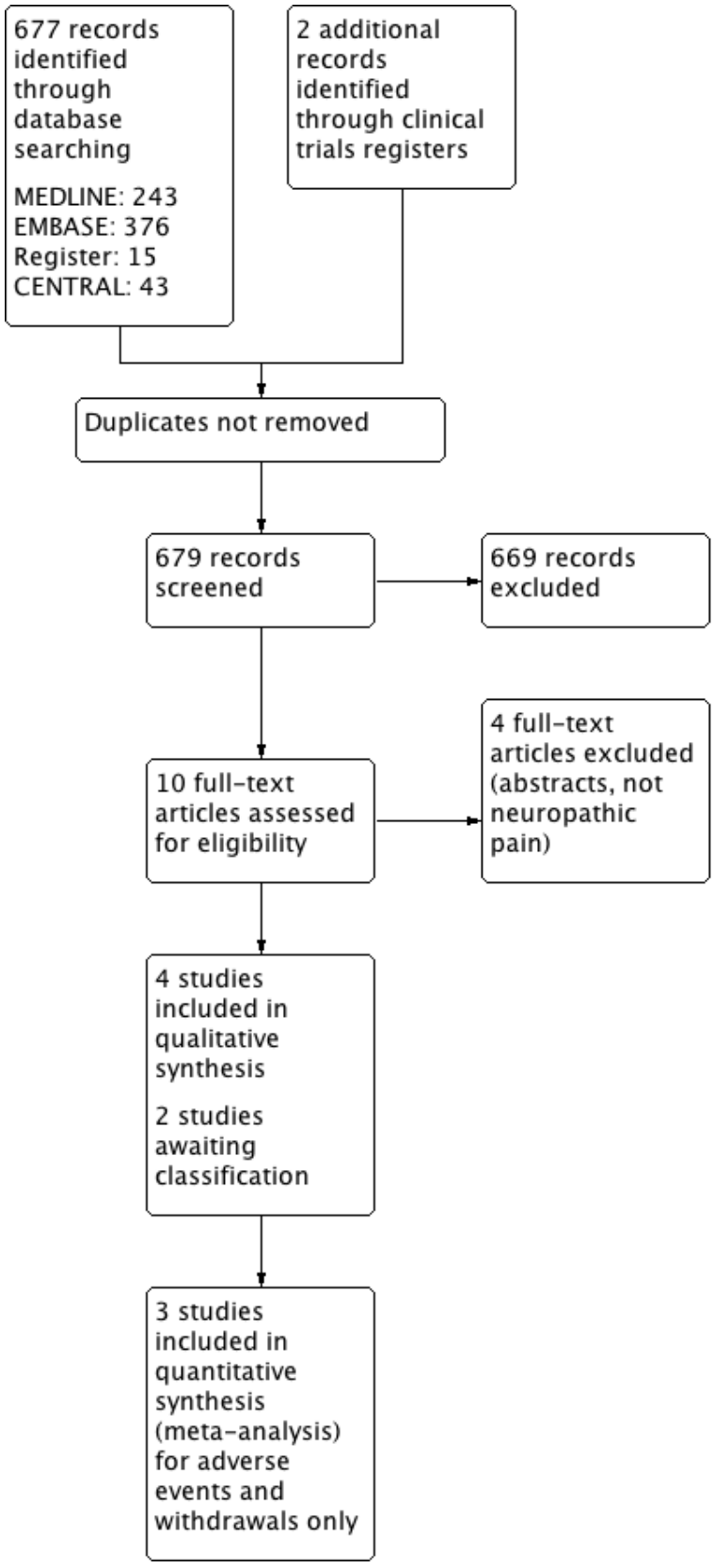
## Data collection and analysis

The intention was to perform separate analyses according to particular neuropathic pain conditions or fibromyalgia. Analyses combining different neuropathic pain conditions would be done for exploratory purposes only.

### Selection of studies

We determined eligibility by reading the abstract of each study identified by the search. We eliminated studies that clearly did not satisfy inclusion criteria, and we obtained full copies of the remaining studies; two review authors made decisions. Two review authors read these studies independently and reached agreement by discussion. We did not anonymise the studies in any way before assessment. We created a PRISMA (Preferred Reporting Items for Systematic Reviews) flow chart to illustrate the study selection process (Figure 1).

**Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews) flow chart.**



### Data extraction and management

Two review authors independently extracted data using a standard form and checked for agreement before entry into Review Manager (RevMan) (RevMan 2012) or any other analysis tool. We included information about the pain condition and number of participants treated, drug and dosing regimen, study design (placebo or active control), study duration and follow-up, analgesic outcome measures and results, withdrawals, and adverse events (participants experiencing any adverse event or serious adverse event).

### Assessment of risk of bias in included studies

We used the Oxford Quality Score (Jadad 1996) as the basis for inclusion, limiting inclusion to studies that were, as a minimum, randomised and double-blind.

Two authors independently assessed risk of bias for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and adapted from those used by the Cochrane Pregnancy and Childbirth Group, with any disagreements resolved by discussion. We assessed the following for each study.

1. Random sequence generation (checking for possible selection bias). We assessed the method used to generate the allocation sequence as: low risk of bias (any truly random process, for example random number table; computer random number generator); unclear risk of bias (method used to generate sequence not clearly stated). We excluded studies using a non-random process (for example, odd or even date of birth; hospital or clinic record number).
2. Allocation concealment (checking for possible selection bias). The method used to conceal allocation to interventions prior to assignment determines whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. We assessed the methods as: low risk of bias (for example, telephone or central randomisation; consecutively numbered sealed opaque envelopes); unclear risk of bias (method not clearly stated). We excluded studies that did not conceal allocation (for example, open list).
3. Blinding of outcome assessment (checking for possible detection bias). We assessed the methods used to blind study participants and outcome assessors from knowledge of which intervention a participant received as: low risk of bias (study states that it was blinded and describes the method used to achieve blinding, for example, identical tablets; matched in appearance and smell); unclear risk of bias (study states that it was blinded but does not provide an adequate description of how it was achieved). We excluded studies that were not double-blind.
4. Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data). We assessed the methods used to deal with incomplete data as: low risk (< 10% of participants did not complete the study and/or used ‘baseline observation carried forward’ analysis); unclear risk of bias (used 'last observation carried forward' (LOCF) analysis); high risk of bias (used 'completer' analysis).
5. Size of study (checking for possible biases confounded by small size). We assessed studies as being at low risk of bias (≥ 200 participants per treatment arm); unclear risk of bias (50 to 199 participants per treatment arm);high risk of bias (< 50 participants per treatment arm).

### Measures of treatment effect

We calculated the number needed to treat for an additional beneficial outcome (NNTB) as the reciprocal of the absolute risk reduction (ARR) (McQuay 1998). For unwanted effects, the NNTB becomes the number needed to treat for an additional harmful outcome (NNTH) and is calculated in the same manner. We used dichotomous data to calculate risk ratios (RR) with 95% confidence intervals (CI) using a fixed-effect model unless significant statistical heterogeneity was found (see below). We did not use continuous data in analyses.

### Unit of analysis issues

The control treatment arm would be split between active treatment arms in a single study if the active treatment arms were not combined for analysis.

### Dealing with missing data

We used intention-to-treat (ITT) analysis where the ITT population consisted of participants who were randomised, took at least one dose of the assigned study medication, and provided at least one post-baseline assessment. Missing participants were assigned zero improvement.

### Assessment of heterogeneity

We dealt with clinical heterogeneity by combining studies that examined similar conditions. We assessed statistical heterogeneity visually (L'Abbé 1987) and with the use of the $I^2$ statistic. When $I^2$ was greater than 50%, we planned to consider possible reasons.

### Assessment of reporting biases

The aim of this review was to use dichotomous data of known utility (Moore 2010b). The review did not depend on what authors of the original studies chose to report or not, though clearly difficulties arose in studies failing to report any dichotomous results. If useful, we extracted and used continuous data, which probably poorly reflect efficacy and utility, but did so for illustrative purposes only.

We assessed publication bias using a method designed to detect the amount of unpublished data with a null effect required to make any result clinically irrelevant (in this case an NNTB of 10 or higher) (Moore 2008).

### Data synthesis

We used a fixed-effect model for meta-analysis.

We analysed efficacy data for each painful condition in two tiers, according to outcome and freedom from known sources of bias.

- The first tier used data that met current best standards, where studies report the outcome of at least 50% pain intensity reduction over baseline (or its equivalent) without the use of LOCF or other imputation method for dropouts; report an ITT analysis; last eight to 12 weeks or longer; have a parallel group design; and have at least 200 participants (preferably at least 400) in the comparison. We reported these top tier results first.
- The second tier used any available data, but where one or more of the above conditions were not met, for example, reporting at

least 30% pain intensity reduction; using LOCF or a completer analysis; lasting four to eight weeks; and where the numbers of participants and studies were small.

### Subgroup analysis and investigation of heterogeneity

We planned for all analyses to be according to individual painful conditions, because placebo response rates with the same outcome can vary between conditions, as can the drug-specific effects (Moore 2009). We did not plan subgroup analyses since experience of previous reviews indicated that there would be too few data for any meaningful subgroup analysis.

### Sensitivity analysis

We planned no sensitivity analysis because the evidence base was known to be too small to allow reliable analysis, and we decided that results from neuropathic pain of different origins would not be pooled in the primary analyses. We would have examined details of dose escalation schedules in the unlikely situation that these could have provided some basis for a sensitivity analysis.

## RESULTS

## Description of studies

### Results of the search

Searches found 679 possible titles, which we examined for possible inclusion (Figure 1). We examined 10 in detail. We included four and excluded four. One further study (Wang 2011) was a meta-analysis of six Chinese-language studies of topiramate in trigeminal neuralgia. The methodological quality of the individual studies was described as poor, and so we placed the report into the category of awaiting classification, as none of the individual studies were obtainable. We identified another study in orofacial pain, but could find no results (NCT00001725).

### Included studies

We included four studies, three in painful diabetic neuropathy (1643 participants: NCT00231673; Raskin 2004; Thienel 2004) and one in lumbar radiculopathy (41 participants: Khoromi 2005). Thienel 2004 reported on 1259 participants from three separate randomised trials, mainly as pooled data.

The mean age of participants in the studies was 58 to 59 years, and the proportion of men was 50% to 58%.

Participants with painful diabetic neuropathy had bilateral symptoms (Raskin 2004; Thienel 2004), had been on stable anti-diabetic treatment regimens for at least three months with HbA1c ≤ 11% (≤ 97 mmol/mol), and had pain of at least 4/10 (numerical rating scale) at baseline, following analgesic washout. NCT00231673 recruited participants with at least mild pain, but did not report the actual pain scores at the start of treatment. Participants with lumbar radiculopathy had pain in one or both buttocks or legs associated with one or more features of radiculopathy (for example, sharp shooting pain below the knee, imaging evidence of nerve compression in the lumbar region), and had average leg pain of at least 4/10 for the past month. In all cases, pain had been present for at least three months.

The dose of topiramate was titrated in all studies. NCT00231673 titrated to 200 mg/day over six weeks. Khoromi 2005 used a 50 mg starting dose and titrated to a maximum of 400 mg/day over four weeks, followed by a two-week maintenance period at the maximum tolerated, or target, dose. Raskin 2004 started at 25 mg/day, titrating to a maximum of 400 mg/day over eight weeks, followed by a four-week maintenance period. Thienel 2004 also started at 25 mg/day, titrating to a maximum of 100 mg/day, 200 mg/day, or 400 mg/day over six to 10 weeks, depending on the target dose, followed by a 12-week maintenance period.

NCT00231673, Raskin 2004, and Thienel 2004 were parallel studies and used an inert placebo, while Khoromi 2005 was a two-period cross-over study with a two-week dose-tapering washout between periods, and used an active placebo (diphenhydramine) to mimic possible adverse events of topiramate.

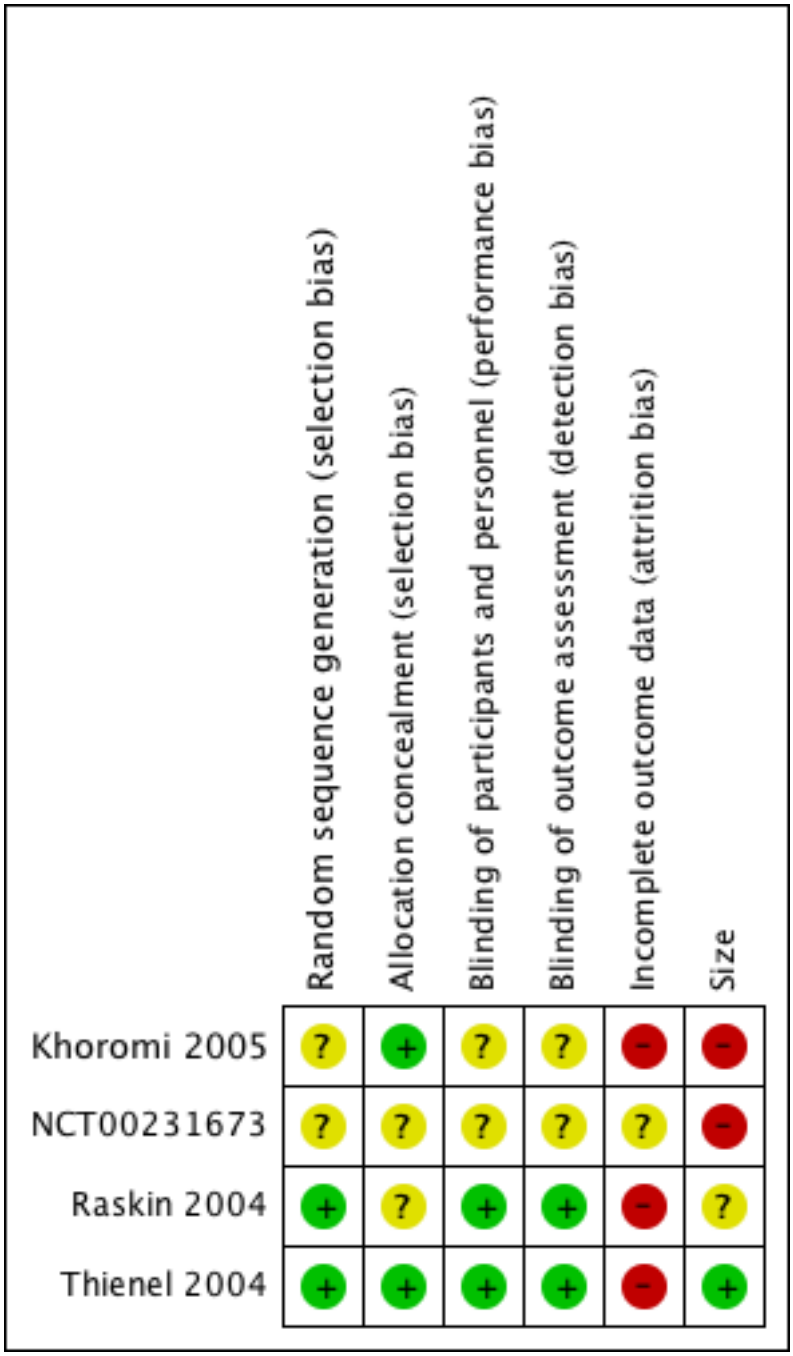
### Excluded studies

We excluded one study after reading the full text (Muehlbacher 2006) as participants had back pain that was not specifically of neuropathic origin. Three other excluded studies appeared as short conference abstracts (Edwards 1998; Edwards 2000; Vinik 2003) and may have formed part of Thienel 2004.

## Risk of bias in included studies

Each study had at least one source of high risk of bias. Figure 2 illustrates the 'Risk of bias' assessments for each included study by category.

**Figure 2. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included study. Red = high risk of bias, yellow = unclear risk of bias, green = low risk of bias.**




### Allocation

All studies were randomised. Raskin 2004 and Thienel 2004 described the method used to produce the random sequence, but only Thienel 2004 described the method used to conceal the allocation. Khoromi 2005 did not describe the method used to generate the sequence, but appeared to have used a remote method to conceal allocation. NCT00231673 provided very little description of methods in a short trial report.

### Blinding

All studies were double-blind. Raskin 2004 and Thienel 2004 described the method used to maintain blinding.

### Incomplete outcome data

Withdrawal rates in all studies were more than 10%. Raskin 2004 and Thienel 2004 reported that they used LOCF in evaluations of pain outcomes for participants who withdrew early, while Khoromi 2005 did not report on treatment of withdrawals in analyses. We

judged all studies to be at high risk of bias for this criterion, with the exception of NCT00231673, where there was an unknown risk.

### Other potential sources of bias

We considered two studies (Khoromi 2005; NCT00231673) to be at high risk of bias due to the small number of participants in each treatment arm.

## Effects of interventions

See: **Summary of findings for the main comparison** Topiramate 200 to 400 mg versus placebo for neuropathic pain

### Efficacy

No study provided first tier evidence for an efficacy outcome.

We judged the following results as second tier because of high withdrawal rates in all studies and use of LOCF imputation (Raskin 2004; Thienel 2004) or less rigorous outcomes and unspecified imputation (Khoromi 2005; NCT00231673).

Details of efficacy outcomes in individual studies are in Appendix 5.

#### *Painful diabetic neuropathy*

NCT00231673 measured pain using VAS scores, but contained almost no information about pain outcomes. The report states that pain scores were not statistically different between topiramate and placebo.

Another study (Raskin 2004) reported dichotomous data for pain relief; 74/208 (36%) participants experienced more than a 50% reduction in pain score from baseline to end of study with topiramate compared to 23/109 (21%) with placebo. For the less rigorous outcome of more than a 30% reduction, there were 103/208 (50%) responders with topiramate and 37/109 (34%) responders with placebo.

The largest study (Thienel 2004) reported only group mean data for pain relief. In the individual studies, the mean and median VAS scores were lower at endpoint than baseline for all treatment groups, by approximately 10/100 to 20/100 points from a baseline of 55/100 to 60/100. The difference between topiramate and placebo was not significant for two of the three studies individually, irrespective of target dose.

#### *Lumbar radiculopathy*

Khoromi 2005 reported the number of participants experiencing at least moderate pain relief, using a six-point PGIC evaluation scale; 15/41 participants had this outcome with topiramate and 7/41 with placebo. We considered this outcome equivalent to ≥ 30% pain reduction.

### Adverse events

For analysis of adverse event outcomes we combined data from participants with different conditions since there is no a priori reason to expect different adverse responses in these different conditions. Details of adverse event outcomes in individual studies are in Appendix 6.

NCT00231673 provided no information about adverse events, but reported, without any analysis presented, that adverse events generally and specific adverse events were more frequent with topiramate than placebo. Two participants (one each in the topiramate and placebo groups) had a serious adverse event.

Two studies (Khoromi 2005; Raskin 2004) contributed data for participants experiencing at least one adverse event (398 participants).

- The proportion of participants with at least one adverse event with topiramate was 82% (204/248, range 82% to 85%).
- The proportion of participants with at least one adverse event with placebo was 71% (106/150).
- The risk ratio for topiramate compared with placebo was 1.2 (95% CI 1.04 to 1.3); the NNTH was 8.6 (95% CI 4.9 to 35) (Analysis 1.1).

Two studies (Raskin 2004; Thienel 2004) contributed data for participants experiencing a serious adverse event (1586 participants). We combined data from the various target doses of topiramate in Thienel 2004.

- The proportion of participants experiencing a serious adverse event with topiramate was 6.6% (72/1093, range 4.8% to 7.0%).
- The proportion of participants experiencing a serious adverse event with placebo was 7.5% (37/493).
- The risk ratio for topiramate compared with placebo was 0.87 (95% CI 0.59 to 1.3); the NNTH was not calculated (Analysis 1.2).

#### *Particular adverse events*

##### Weight loss

NCT00231673 reported average weight loss of 4.1 kg and 0.3 kg with topiramate and placebo, respectively.

Khoromi 2005 did not report on weight loss; three participants in the placebo group and none in the topiramate group reported anorexia as an adverse event.

Raskin 2004 reported a mean weight loss by the final visit in the topiramate group of 2.6 kg, compared to a mean gain of 0.2 kg in the placebo group. With topiramate, 76% experienced weight loss and 17% experienced weight gain, while with placebo, 43% experienced loss and 55% experienced gain.

Thienel 2004 reported that most participants treated with topiramate lost weight. In the groups taking topiramate, 19% to 38% of participants experienced a weight loss by the final visit of ≥ 5% from baseline, compared with 7% of those taking placebo.

##### Other particular adverse events

Other adverse events affecting ≥ 3% of participants included nausea and diarrhoea, fatigue, weakness, sedation and somnolence, dizziness, poor concentration, and paraesthesia.

In participants with diabetic neuropathy, treatment with topiramate did not affect HbA1c levels in Raskin 2004 (including a 26-week open-label follow-up study), but reduced levels (≥ 0.5%) in about 60% of participants in Thienel 2004, compared with 29% of those treated with placebo.

##### Deaths

No deaths linked to treatment were reported. In NCT00231673, one participant died of myocardial infarction three months after stopping placebo, and following spinal surgery.

### Withdrawals

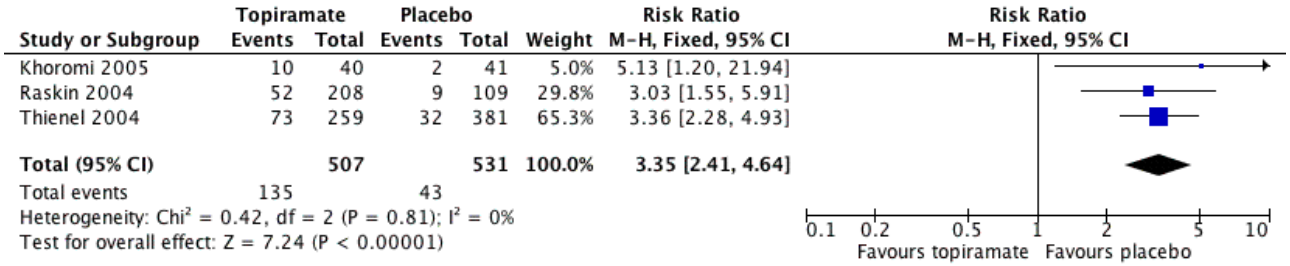
We combined data for the different conditions in analyses of withdrawals. Details of withdrawals in individual studies are in Appendix 6.

#### *Adverse event withdrawals*

All studies contributed data for participants withdrawing because of an adverse event. There appeared to be an increase in adverse event withdrawals with increasing target dose in Thienel 2004, so we have combined data for only 400 mg target doses in this analysis.

- The proportion of participants withdrawing because of an adverse event with topiramate was 27% (135/507, range 25% to 28%).
- The proportion of participants withdrawing because of an adverse event with placebo was 8.1% (43/531, range 4.9% to 8.4%).
- The risk ratio for withdrawal with topiramate compared with placebo was 3.4 (95% CI 2.4 to 4.7); the NNTH was 5.4 (95% CI 4.3 to 7.1) (Analysis 1.3; Figure 3).

**Figure 3. Forest plot of comparison: 1 Topiramate versus placebo, outcome: 1.3 Adverse event withdrawals.**




Including data for the 200 mg target dose in Thienel 2004 did not change the result: RR 3.2 (95% CI 2.4 to 4.3), NNTH 5.6 (95% CI 4.6 to 7.0), 1407 participants.

#### *Lack of efficacy withdrawals*

All studies contributed data for participants withdrawing because of lack of efficacy. There appeared to be a decrease in lack of efficacy withdrawals with increasing target dose in Thienel 2004, so we combined data for only 400 mg target doses in this analysis.

- The proportion of participants withdrawing because of lack of efficacy with topiramate was 12% (63/507, range 0% to 12%).
- The proportion of participants withdrawing because of lack of efficacy with placebo was 18% (98/531, range 0% to 22%).
- The risk ratio for withdrawal with topiramate compared with placebo was 0.68 (95% CI 0.50 to 0.93); the NNTB to prevent a lack of efficacy withdrawal was 17 (95% CI 9.6 to 60) (Analysis 1.4).

Inclusion of data for the 200 mg target dose in Thienel 2004 did not change the result: RR 0.67 (95% CI 0.52 to 0.86), NNTB to prevent a lack of efficacy withdrawal 18 (95% CI 10 to 59), 1407 participants.

## DISCUSSION

### Summary of main results

The review found four studies, with 1684 participants, testing topiramate in two different conditions. The largest study failed to find any difference between topiramate and placebo at various doses between 100 mg and 400 mg daily. The two small studies found minimal arithmetic improvement of topiramate over placebo, despite having data treatments that were the source of significant potential positive bias. Participants given topiramate experienced more adverse events, but not serious adverse events, than placebo, and adverse event withdrawal was much higher with topiramate than placebo, affecting 27% of participants.

There was no evidence of benefit given the potentially large biases in the way results were reported (see below); many participants withdrew from the trial because of adverse events (see Summary of findings for the main comparison).

### Overall completeness and applicability of evidence

The overall completeness and applicability of the evidence was poor. Topiramate was tested only in painful diabetic neuropathy in any numbers, and the reporting of the three studies in 1643 participants could have made estimation of efficacy better, but reporting failures limited this.

### Quality of the evidence

The quality of the evidence was generally good, but data handling biases, small size, or both, compromised all three studies. The major potential bias was the use of LOCF imputation in the two largest studies and an incomplete description in the third, smallest, study. Adverse event withdrawals were 27% with topiramate and 8% with placebo, a 19% absolute difference. It has been estimated that a difference of this magnitude would be associated with an overestimation of treatment effects of around 200% (Moore 2012a). This is major potential for bias when only trivial evidence of benefit indicates strongly that topiramate is likely to be of no benefit.

### Potential biases in the review process

We know of no potential biases in the review process.

### Agreements and disagreements with other studies or reviews

Carroll 2004 suggested that topiramate had been used successfully to treat painful diabetic neuropathy, based mainly on case reports, retrospective case series, open-label studies, and abstracts of two randomised trials that seem not to have been published, except probably as part of a pooled analysis (Thienel 2004). The meta-analysis of Wang 2011 of topiramate in trigeminal neuralgia in 354 participants (which appears to be of poor quality, but awaits

translation and analysis of the Chinese trials therein) found no benefit over placebo after one month. A systematic review of drugs for painful diabetic neuropathy indicated that topiramate was the least effective drug examined, despite failing to acknowledge bias from imputation methods (Snedecor 2014). The results are also in broad agreement with the conclusions drawn by European guidelines (Attal 2010). A systematic review of antiepileptic drugs for painful diabetic neuropathy did conclude that topiramate was effective, based on a single study and inadequate methods (Gutierrez-Alvarez 2007).

Of interest is the observation in an open-label extension trial that patients taking topiramate and obtaining pain relief continue to do so over up to six months, though adverse event withdrawals continue at a high rate (Donofrio 2005). The weakness of this study was that it only reported average pain scores, and individual patient data analysis would be more insightful. This is fertile ground for a discussion of the relevance or otherwise of open-label extension studies and their relationship to efficacy from the randomised, double-blind phase of a clinical trial.

## AUTHORS' CONCLUSIONS

### Implications for practice

There is no evidence that topiramate is effective in treating diabetic neuropathic pain or fibromyalgia. Use of topiramate should be restricted to experienced pain physicians in particular clinical situations.

### Implications for research

There is sufficient evidence that topiramate is ineffective to make further research in this area unnecessary, with the possible exception of retrospective individual patient data analysis from studies already completed, in order to generate hypotheses and insights.

## ACKNOWLEDGEMENTS

Dr Sivakumar Sathasivam and Prof Turo Nurmikko, authors of the first published version of the protocol for this review.

The editorial base of the Cochrane Neuromuscular Disease Group is supported by the MRC Centre for Neuromuscular Diseases.

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Soni A, Batra R, Gwilym S, Spector T, Hart D, Arden N, et al. Neuropathic features of joint pain: a community-based study. *Arthritis & Rheumatism* 2013;**65**(7):1942-9. [DOI: 10.1002/art.37962]

**Straube 2008**

Straube S, Derry S, McQuay HJ, Moore RA. Enriched enrollment: definition and effects of enrichment and dose in trials of pregabalin and gabapentin in neuropathic pain. A systematic review. *British Journal of Clinical Pharmacology* 2008;**66**(2):266-75. [DOI: 10.1111/j.1365-2125.2008.03200.x]

**Straube 2010**

Straube S, Derry S, Moore RA, Paine J, McQuay HJ. Pregabalin in fibromyalgia--responder analysis from individual patient data. *BMC Musculoskeletal Disorders* 2010;**11**:150. [DOI: 10.1186/1471-2474-11-150]

**Sultan 2008**

Sultan A, Gaskell H, Derry S, Moore RA. Duloxetine for painful diabetic neuropathy and fibromyalgia pain: systematic review of randomised trials. *BMC Neurology* 2008;**8**:29. [DOI: 10.1186/1471-2377-8-29]

**Sun 2006**

Sun C, Lay C, Broner S, Silberstein S, Tepper S, Newman L. Reversible anorgasmia with topiramate therapy for headache: a report of 7 patients. *Headache* 2006;**46**(9):1450-3. [DOI: 10.1111/j.1526-4610.2006.00587.x]

**Torrance 2006**

Torrance N, Smith BH, Bennett MI, Lee AJ. The epidemiology of chronic pain of predominantly neuropathic origin. Results from a general population survey. *Journal of Pain* 2006;**7**(4):281-9. [DOI: 10.1016/j.jpain.2005.11.008]

**Tracey 2011**

Tracey I. Can neuroimaging studies identify pain endophenotypes in humans?. *Nature Reviews. Neurology* 2011;**7**(3):173-81. [DOI: 10.1038/nrneurol.2011.4]

**Treede 2008**

Treede RD, Jensen TS, Campbell JN, Cruccu G, Dostrovsky JO, Griffin JW, et al. Neuropathic pain: redefinition and a grading system for clinical and research purposes. *Neurology* 2008;**70**(18):1630-5. [DOI: 10.1212/01.wnl.0000282763.29778.59]

**Vos 2012**

Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;**380**(9859):2163-96. [DOI: 10.1016/S0140-6736(12)61729-2]

**Walia 2004**

Walia KS, Khan EA, Ko DH, Raza SS, Khan YN. Side effects of antiepileptics - a review. *Pain Practice* 2004;**4**(3):194-203. [PUBMED: 17173601]

**Wiffen 2010**

Wiffen PJ, Collins S, McQuay HJ, Carroll D, Jadad A, Moore RA. Anticonvulsant drugs for acute and chronic pain. *Cochrane Database of Systematic Reviews* 2010, Issue 1. [DOI: 10.1002/14651858.CD001133.pub3]

**Wiffen 2011a**

Wiffen PJ, Derry S, Moore RA, McQuay HJ. Carbamazepine for acute and chronic pain in adults. *Cochrane Database of Systematic Reviews* 2011, Issue 1. [DOI: 10.1002/14651858.CD005451.pub2]

**Wiffen 2011b**

Wiffen PJ, Derry S, Moore RA. Lamotrigine for acute and chronic pain. *Cochrane Database of Systematic Reviews* 2011, Issue 2. [DOI: 10.1002/14651858.CD006044.pub3]

**Wolfe 1990**

Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis and Rheumatism* 1990;**33**(2):160-72. [PUBMED: 2306288]

**Wolfe 2010**

Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Katz RS, Mease P, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care & Research* 2010;**62**(5):600-10. [DOI: 10.1002/acr.20140]

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies *[ordered by study ID]*

**Khoromi 2005**

| | |
|---|---|
| Methods | Single-centre, randomised, double-blind, active, placebo (diphenhydramine)-controlled<br>Two-period cross-over study: 4-week titration, 2-week maintenance, 2-week washout with dose taper, then cross-over |
| Participants | Lumbar radiculopathy ≥ 3 months<br>Average pain ≥ 4/10 in past month<br>Mean age ˜58 years (28 to 74)<br>M 23, F 20<br>N = 41 (1 participant ineligible, 1 participant dropped out prior to randomisation) |
| Interventions | Topiramate to maximum 400 mg/day<br><br>Placebo<br><br>Titration to maximum tolerated dose over 4 weeks: topiramate starting at 50 mg in the evening, increasing by 50 mg increments, or diphenhydramine starting at 6.25 mg, increasing to maximum 25 mg twice daily |
| Outcomes | 1. Mean score for average leg pain during maintenance, based on daily pain records (0 to 10)<br>2. PGIC (leg and back) pain (worse, none, slight, moderate, a lot, complete). ≥ moderate = responder<br>3. Oswestry Low Back Pain Disability Questionnaire<br>4. Beck Depression Inventory<br>5. Short Form-36 Health Survey<br><br>Imputation not mentioned |
| Notes | Oxford Quality Score: R1, DB1, W1. Total = 3/5 |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Method not described |
| Allocation concealment (selection bias) | Low risk | "independent (NIH) pharmacist" |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | No details given. "Patients and research staff were blinded to the randomization order" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | No details given. "Patients and research staff were blinded to the randomization order" |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | > 10% withdrawals with active treatment. Imputation not mentioned |

**Khoromi 2005** *(Continued)*

| | | |
|---|---|---|
| Size | High risk | < 50 participants per treatment arm |

**NCT00231673**

| | |
|---|---|
| Methods | Multicentre, randomised, double-blind, placebo-controlled, parallel group study<br>Duration 18 weeks, consisting of 6-week titration and 12-week maintenance periods |
| Participants | Diabetic peripheral polyneuropathy<br>Current pain at least mild<br>Age 18 to 75 years<br>Duration of condition 6 months or longer |
| Interventions | Topiramate 200 mg/day or placebo |
| Outcomes | 1. Pain intensity - VAS and categorical scales<br>2. Adverse events |
| Notes | Main focus of study was nerve conduction |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not described |
| Allocation concealment (selection bias) | Unclear risk | Not described |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Not described |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Not described |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Not described |
| Size | High risk | Fewer than 50 participants in treatment arm |

**Raskin 2004**

| | |
|---|---|
| Methods | Multicentre, randomised, double-blind, placebo-controlled<br>Parallel groups: up to 28-day washout, 8-week dose titration, 4-week maintenance dose |
| Participants | Symmetric diabetic peripheral neuropathy > 3 months, < 10 years |

**Raskin 2004** *(Continued)*

| | |
|---|---|
| | Diabetic control stable ≥ 3 months, with HbA1c ≤ 11%<br>Baseline pain ≥ 4/10 after washout<br><br>Exclude: history of failure of topiramate for a painful condition<br><br>Mean age 59 (± 10) years<br>M 157, F 160<br><br>N = 317 |
| Interventions | Topiramate to maximum 400 mg/day, n = 208<br><br>Placebo, n = 109<br><br>Titration to maximum tolerated dose: topiramate 25 mg in evening increasing by 25 mg/day in weeks 2 to 4, 50 mg in weeks 5 and 6, and 100 mg in weeks 7 and 8<br>Dose tapered if participant left study<br><br>Rescue medication (500 mg paracetamol or similar) available for first 6 weeks only and not within 24 hours of any study visit<br>Mean daily dose (maintenance) of topiramate: 320 mg |
| Outcomes | 1. Pain intensity on 100 mm VAS. Mean and responder = > 30% and > 50% reduction in score<br>2. Current pain on 5-point categorical scale (none, mild, moderate, severe, extreme)<br>3. Worst pain in last week on 5-point categorical scale<br>4. SF-36<br>5. Sleep disruption on 0 to 10-point scale<br>6. PGIC on 5-point scale (poor, fair, good, very good, excellent)<br><br>Imputation - primary efficacy used LOCF, then compared with analysis using weighting by inverse of probability of completing (for completers) |
| Notes | Oxford Quality Score: R2, DB2, W1. Total = 5/5 |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Computer-generated, balanced blocks |
| Allocation concealment (selection bias) | Unclear risk | Not described. Investigators assigned treatment sequentially |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | "identically appearing placebo tablets" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | "identically appearing placebo tablets" |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | > 10% withdrawals. Imputation - primary efficacy analysis used LOCF |
| Size | Unclear risk | 208 (topiramate) and 109 (placebo) participants |

**Thienel 2004**

| | |
|---|---|
| Methods | Multicentre, randomised, double-blind, placebo-controlled<br>Parallel groups: up to 28-day baseline/washout, 6- to 10-week titration (depending on target dose), 12-week maintenance dose<br><br>Three studies combined and published in one report |
| Participants | Bilateral diabetic peripheral neuropathy ≥ 6 months<br>Diabetic control stable ≥ 3 months, with HbA1c ≤ 11%<br>Baseline pain ≥ moderate after washout (scale 0 to 4: none, mild, moderate, severe, extreme)<br><br>Mean age 58 (± 10) years (21 to 81)<br>M 733, F 536<br><br>N = 1269 (ITT= 1259) |
| Interventions | Topiramate to maximum 100 mg/day, n = 253<br><br>Topiramate to maximum 200 mg/day, n = 372<br><br>Topiramate to maximum 400 mg/day, n = 260<br><br>Placebo, n = 384<br><br>Titration: topiramate 25 mg/day in evening, increasing in 25 mg increments to 100 mg/day, then in weekly 50 mg increments to target dose or maximum tolerated dose<br><br>Short-acting immediate-release analgesics permitted as rescue medication during double-blind treatment |
| Outcomes | 1. Pain intensity on 100 mm VAS (mean and median reported for each trial. Change from baseline to final visit reported)<br>2. Current pain on 5-point categorical scale (none, mild, moderate, severe, extreme)<br>3. Worst pain in last week on 5-point categorical scale<br>4. Sleep disruption on 0 to 10-point scale<br>5. SF-36<br><br>Pain evaluations used LOCF for early withdrawal |
| Notes | Oxford Quality Score: R2, DB2, W1. Total = 5/5 |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Computer-generated by study sponsor, balanced, stratified by centre |
| Allocation concealment (selection bias) | Low risk | Not described, but judged likely to be remote allocation because of central generation of randomised sequence |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | "Study medications were identical in appearance and packaged in identical containers" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | "Study medications were identical in appearance and packaged in identical containers" |

**Thienel 2004** *(Continued)*

| | | |
|---|---|---|
| Incomplete outcome data (attrition bias) All outcomes | High risk | > 10% withdrawals. Imputation for pain evaluations - LOCF for early withdrawal |
| Size | Low risk | > 200 participants per treatment arm |

DB: double-blind; ITT: intention-to-treat; LOCF: last observation carried forward; N: total number of participants in comparison; n: number of participants in treatment group; PGIC: Patient Global Impression of Change; R: randomisation; VAS: visual analogue scale; W: withdrawals.

## Characteristics of excluded studies *[ordered by study ID]*

| Study | Reason for exclusion |
|---|---|
| Edwards 1998 | Abstract |
| Edwards 2000 | Abstract |
| Muehlbacher 2006 | Not specifically neuropathic pain |
| Vinik 2003 | Abstract |

## Characteristics of studies awaiting assessment *[ordered by study ID]*

**NCT00001725**

| | |
|---|---|
| Methods | Possibly randomised cross-over study of topiramate and dextromethorphan (estimated 100 participants) |
| Participants | Orofacial pain and trigeminal pain |
| Interventions | Topiramate, dextromethorphan |
| Outcomes | Not known |
| Notes | Reported as completed, but without study results |

**Wang 2011**

| | |
|---|---|
| Methods | Meta-analysis of randomised trials (six trials, 354 participants) |
| Participants | Trigeminal neuralgia |
| Interventions | Topiramate, carbamazepine |
| Outcomes | Not known, undefined efficacy |
| Notes | Chinese-language studies described as of poor quality |

## DATA AND ANALYSES

### Comparison 1. Topiramate versus placebo

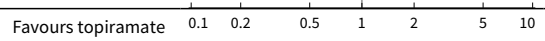
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Any adverse event | 2 | 398 | Risk Ratio (M-H, Fixed, 95% CI) | 1.17 [1.04, 1.31] |
| 2 Serious adverse events | 2 | 1586 | Risk Ratio (M-H, Fixed, 95% CI) | 0.87 [0.59, 1.27] |
| 3 Adverse event withdrawals | 3 | 1038 | Risk Ratio (M-H, Fixed, 95% CI) | 3.35 [2.41, 4.64] |
| 4 Lack of efficacy withdrawals | 3 | 1038 | Risk Ratio (M-H, Fixed, 95% CI) | 0.68 [0.50, 0.93] |

### Analysis 1.1. Comparison 1 Topiramate versus placebo, Outcome 1 Any adverse event.

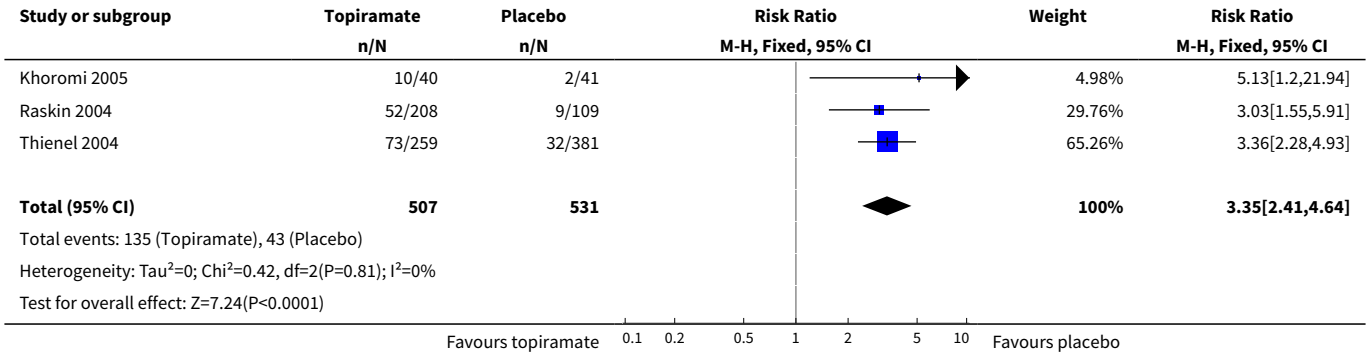
| Study or subgroup | Topiramate n/N | Placebo n/N | Risk Ratio M-H, Fixed, 95% CI | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|
| Khoromi 2005 | 34/40 | 29/41 | | 22.09% | 1.2[0.95,1.52] |
| Raskin 2004 | 170/208 | 77/109 | | 77.91% | 1.16[1.01,1.33] |
| **Total (95% CI)** | **248** | **150** | | **100%** | **1.17[1.04,1.31]** |
| Total events: 204 (Topiramate), 106 (Placebo) | | | | | |
| Heterogeneity: $Tau^2$=0; $Chi^2$=0.07, df=1(P=0.78); $I^2$=0% | | | | | |
| Test for overall effect: Z=2.55(P=0.01) | | | | | |


### Analysis 1.2. Comparison 1 Topiramate versus placebo, Outcome 2 Serious adverse events.

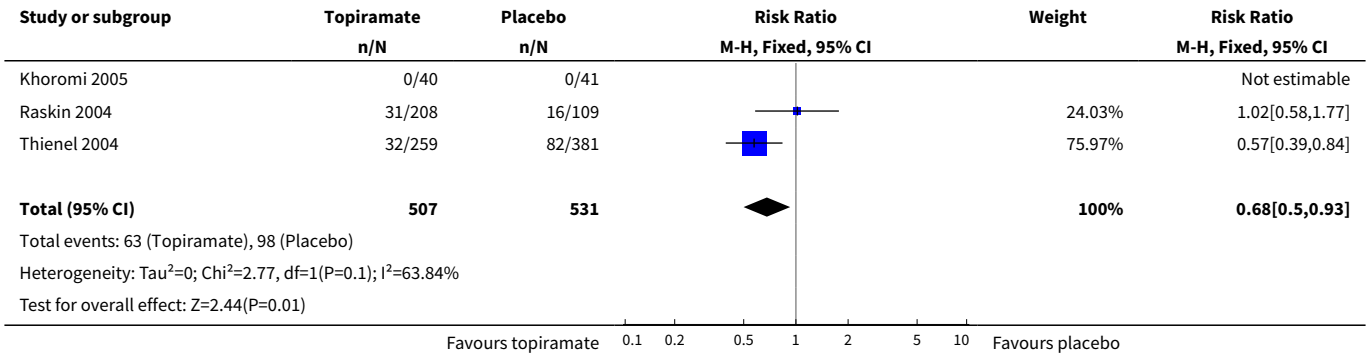
| Study or subgroup | Topiramate n/N | Placebo n/N | Risk Ratio M-H, Fixed, 95% CI | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|
| Raskin 2004 | 10/208 | 6/109 | | 15.4% | 0.87[0.33,2.34] |
| Thienel 2004 | 62/885 | 31/384 | | 84.6% | 0.87[0.57,1.31] |
| **Total (95% CI)** | **1093** | **493** | | **100%** | **0.87[0.59,1.27]** |
| Total events: 72 (Topiramate), 37 (Placebo) | | | | | |
| Heterogeneity: $Tau^2$=0; $Chi^2$=0, df=1(P=0.99); $I^2$=0% | | | | | |
| Test for overall effect: Z=0.72(P=0.47) | | | | | |



**Analysis 1.3. Comparison 1 Topiramate versus placebo, Outcome 3 Adverse event withdrawals.**




**Analysis 1.4. Comparison 1 Topiramate versus placebo, Outcome 4 Lack of efficacy withdrawals.**




# APPENDICES

## Appendix 1. Methodological considerations in chronic pain

There have been several recent changes in how efficacy of conventional and unconventional treatments is assessed in chronic painful conditions. The outcomes are now better defined, particularly with new criteria of what constitutes moderate or substantial benefit (Dworkin 2008); older trials may only report participants with "any improvement". Newer trials tend to be larger, avoiding problems from the random play of chance. Newer trials also tend to be longer, up to 12 weeks, and longer trials provide a more rigorous and valid assessment of efficacy in chronic conditions. New standards have evolved for assessing efficacy in neuropathic pain, and we are now applying stricter criteria for inclusion of trials and assessment of outcomes, and are more aware of problems that may affect our overall assessment. To summarise some of the recent insights that must be considered in this new review:

1. Pain results tend to have a bimodal rather than a normal distribution; the majority of patients have either very poor pain relief or very good pain relief. This is true in acute pain (Moore 2011a; Moore 2011b), back pain (Moore 2010c), and arthritis (Moore 2010d), as well as in neuropathic pain (Moore 2012b) and fibromyalgia (Straube 2010); in all cases mean results usually describe the experience of almost no-one in the trial. Data expressed as averages are potentially misleading, unless they can be proven to be suitable.
2. As a consequence, we have to depend on dichotomous results (the individual either has or does not have the outcome) usually from pain changes or patient global assessments. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) group has helped with their definitions of minimal, moderate, and substantial improvement (Dworkin 2008). In arthritis, trials shorter than 12 weeks, and especially those shorter than eight weeks, overestimate the effect of treatment (Moore 2010b); the effect is particularly strong for less effective analgesics, and this may also be relevant in neuropathic-type pain.
3. The proportion of patients with at least moderate benefit can be small, even with an effective medicine, falling from 60% with an effective medicine in arthritis to 30% in fibromyalgia (Moore 2009; Moore 2010b; Straube 2008; Sultan 2008). A Cochrane review of pregabalin in neuropathic pain and fibromyalgia demonstrated different response rates for different types of chronic pain (higher in diabetic neuropathy and postherpetic neuralgia and lower in central pain and fibromyalgia) (Moore 2009). This indicates that different

neuropathic pain conditions should be treated separately from one another, and that pooling should not be done unless there are good grounds for doing so.

4. Finally, a presently unpublished review summarises data that patients who get good pain relief (moderate or better) have major benefits in many other outcomes, affecting quality of life in a significant way (Moore 2014).

## Appendix 2. MEDLINE (OvidSP) search strategy

Database: Ovid MEDLINE(R) <1946 to April Week 4 2013>
Search Strategy:
---
1 randomized controlled trial.pt. (347234)
2 controlled clinical trial.pt. (85791)
3 randomized.ab. (249775)
4 placebo.ab. (137573)
5 drug therapy.fs. (1604676)
6 randomly.ab. (178756)
7 trial.ab. (257566)
8 groups.ab. (1162225)
9 or/1-8 (2996005)
10 exp animals/ not humans.sh. (3806377)
11 9 not 10 (2546275)
12 (topiramate or Topamax).mp. (2913)
13 exp Pain/ (288260)
14 Fibromyalgia/ (5775)
15 (pain$ or fibromyalgi$ or neuralgi$ or analgesi$ or discomfort$).mp. (545976)
16 or/13-15 (614199)
17 11 and 12 and 16 (256)
18 remove duplicates from 17 (243)

## Appendix 3. EMBASE (OvidSP) search strategy

Database: Embase <1980 to 2013 Week 18>
Search Strategy:
---
1 crossover-procedure/ (36788)
2 double-blind procedure/ (114409)
3 randomized controlled trial/ (341619)
4 single-blind procedure/ (17333)
5 (random$ or factorial$ or crossover$ or cross over$ or cross-over$ or placebo$ or (doubl$ adj blind$) or (singl$ adj blind$) or assign$ or allocat$ or volunteer$).tw. (1223171)
6 or/1-5 (1303139)
7 exp animals/ (18232689)
8 exp humans/ (14316232)
9 7 not (7 and 8) (3916457)
10 6 not 9 (1170893)
11 limit 10 to embase (913682)
12 (topiramate or topamax).mp. (13964)
13 11 and 12 (1778)
14 fibromyalgia/ (12039)
15 exp neuralgia/ (65239)
16 (pain$ or fibromyalgi$ or neuralgi$ or analgesi$ or discomfort$).mp. (873715)
17 or/14-16 (891352)
18 11 and 12 and 17 (377)
19 remove duplicates from 18 (376)

## Appendix 4. CENTRAL search strategy

#1 topiramate or topamax
#2 MeSH descriptor: [Pain] explode all trees
#3 pain* or fibromyalgi* or neuralgi* or analgesi* or discomfort*
#4 #2 or #3
#5 #1 and #4

## Appendix 5. Summary of efficacy in individual studies

| Study | Treatment | Pain outcome | Other efficacy outcome |
|---|---|---|---|
| NCT00231673 | Topiramate 200 mg/day, n = 23<br><br>Placebo, n = 24<br><br>Titration over 6 weeks | There was no statistically significant difference in the mean change in VAS scores between the Top group and the Placebo group (P = 0.354) | No significant difference between topiramate and placebo for change from baseline in peroneal motor nerve conduction velocity |
| Khoromi 2005 | Topiramate to maximum 400 mg/day, n = 41<br>Placebo (diphenhydramine) to maximum 50 mg/day, n = 41<br><br>Titration over 4 weeks | PGIC improvement in leg and back pain, ≥ moderate<br>Topiramate: 15/41<br>Placebo: 7/41 | Percent pain reduction<br>Scores were significantly better on topiramate than placebo for average back pain, average overall pain, and worst overall pain, and they showed a trend toward pain reduction for worst back pain<br><br>Depression, disability, and SF-36 categories did not show significant difference between groups |
| Raskin 2004 | Topiramate to maximum 400 mg/day, n = 208<br>Placebo, n = 109<br><br>Titration over 8 weeks | > 50% PI reduction<br>Topiramate: 74/208<br>Placebo: 23/109<br><br>> 30% PI reduction<br>Topiramate: 103/208<br>Placebo: 37/109 | PGIC (very good, excellent)<br>Topiramate: 64/208<br>Placebo: 23/109<br><br>PGIC (good, very good, excellent)<br>Topiramate: 112/208<br>Placebo: 37/109<br><br>Mean reduction in sleep disruption:<br>Topiramate: 2.6<br>Placebo: 1.6 |
| Thienel 2004 | Topiramate to maximum 100 mg/day, n = 253<br>200 mg/day, n = 372<br>400 mg/day, n = 260<br>Placebo, n = 384<br><br>Titration over 6 to 10 weeks | In individual studies, mean and median VAS scores lower at endpoint than baseline for all treatment groups. Topiramate versus placebo not significantly different for 2 of 3 studies | No consistent differences between topiramate and placebo for means of other outcomes |

PI: pain intensity; PGIC: Patient Global Impression of Change; SF-36: Short Form-36 Health Survey; VAS: visual analogue scale

## Appendix 6. Summary of adverse events and withdrawals in individual studies

| Study | Treatment | Adverse events | Withdrawals |
|---|---|---|---|
| NCT00231673 | Topiramate 200 mg/day, n = 23<br><br>Placebo, n = 24 | Any AE - not reported<br><br>SAE<br><br>Topiramate: 1/23 (judged of doubtful relationship) | Not reported |

(Continued)

| | | | |
|---|---|---|---|
| | Titration over 6 weeks | Placebo: 1/24 (participant died 3 months later from myocardial infarction following spinal surgery) | |
| Khoromi 2005 | Topiramate to maximum 400 mg/day, n = 41<br>Placebo (diphenhydramine) to maximum 50 mg/day, n = 41<br><br>Titration over 4 weeks | Any AE:<br>Topiramate: 86% = 34/40<br>Placebo: 72% = 29/41<br><br>Most common (≥ 5%):<br>Topiramate: paresthesias, fatigue/weakness, sedation, diarrhoea, headache, constipation, depression, joint pain, leg cramps<br>Placebo: paresthesias, fatigue/weakness, diarrhoea, headache, leg cramps<br><br>Weight not reported: 3 pts in placebo group reported anorexia, none in topiramate group | AE:<br>Topiramate: 7 in period 1, 3 in period 2 = 10/41(24%)<br>Placebo: 1 in period 1, 1 in period 2 = 2/41 (4.9%)<br><br>1 pt dropped out before randomisation<br>1 pt had unrelated cardiac finding in period 1 (placebo) |
| Raskin 2004 | Topiramate to maximum 400 mg/day, n = 208<br>Placebo, n = 109<br><br>Titration over 8 weeks | Any AE:<br>Topiramate: 81% = 170/208<br>Placebo: 71% = 77/109<br><br>SAE:<br>Topiramate: 10/208 (2 judged related to treatment)<br>Placebo: 6/109<br>No deaths<br><br>Most common (≥ 5%):<br>Topiramate: diarrhoea, loss of appetite, somnolence, nausea, upper respiratory tract infection (URTI), paraesthesia, dizziness, fatigue, taste change, sinusitis, headache, poor concentration/attention<br>Placebo: nausea, URTI, dizziness, sinusitis, headache, injury, arthralgia, pain<br><br>Weight change:<br>Topiramate: 76.2% weight loss, 16.5% weight gain<br>Placebo: 43.1% weight loss, 55.0% weight gain<br><br>HbA1c values not changed in either group | AE:<br>Topiramate: 52/208 (25%)<br>Placebo: 9/109 (8.3%)<br><br>LoE:<br>Topiramate: 31/208 (15%)<br>Placebo: 16/109 (15%)<br><br>Other:<br>Topiramate: Pt choice (7), lost to follow up (4), other (8) = 19/208 (9.1%)<br>Placebo: Pt choice (1), lost to follow up (2), other (1) = 4/109 (3.7%) |
| Thienel 2004 | Topiramate to maximum<br>100 mg/day, n = 253<br>200 mg/day, n = 372<br>400 mg/day, n = 260<br>Placebo, n = 384<br><br>Titration over 6 to 10 weeks | Any AE - not reported<br><br>SAE:<br>Topiramate: 7%<br>Placebo 8%<br>No deaths<br><br>Most common (≥ 3%) treatment-limiting AEs (topiramate versus placebo):<br>nausea (4% versus 1%), fatigue (4% versus 0), dizziness (3% versus 2%), poor concentration/attention (3% versus 1%), somnolence (3% versus 1%), appetite decrease (3% versus 0)<br><br>Weight | AE:<br>Topiramate 100 mg: 41/250 (16%)<br>Topiramate 200 mg: 93/369 (25%)<br>Topiramate 400 mg: 73/259 (28%)<br>Placebo 32/381 (8.4%)<br><br>LoE:<br>Topiramate 100 mg: 42/250 (17%)<br>Topiramate 200 mg: 49/369 (13%)<br>Topiramate 400 mg: 32/259 (12%)<br>Placebo 82/381 (22%)<br><br>Other:<br>Topiramate 100 mg: pt choice (18), lost to follow up (8), other (7) = 33/250 (13%) |

(Continued)

| | | |
|---|---|---|
| | Most topiramate-treated pts lost weight: 19% to 38% had ≥ 5% loss over baseline, versus 7% with placebo | Topiramate 200 mg: pt choice (28), lost to follow up (7), other (20) = 55/369 (15%)<br>Topiramate 400 mg: pt choice (19), lost to follow up (11), other (10) = 40/259 (15%)<br>Placebo pt choice (23), lost to follow up (4), other (15) = 42/381 (11%) |

AE: adverse event; LoE: lack of efficacy; pt: participant; SAE: serious adverse event

## WHAT'S NEW

| Date | Event | Description |
|---|---|---|
| 19 February 2016 | Review declared as stable | See Published notes |

## HISTORY

Protocol first published: Issue 1, 2010
Review first published: Issue 8, 2013

| Date | Event | Description |
|---|---|---|
| 30 April 2013 | Amended | New authors. S Sathasivam and T Nurmikko withdrew. |
| 19 April 2013 | Amended | Updated and revised background and methods |

## CONTRIBUTIONS OF AUTHORS

All authors were involved in writing the review.

## DECLARATIONS OF INTEREST

SD and PW have received research support from charities, government, and industry sources at various times, but none relate to this review.

RAM has consulted for various pharmaceutical companies and received lecture fees from pharmaceutical companies related to analgesics and other healthcare interventions, including (in the past five years) AstraZeneca, Eli Lilly and Company, Flynn Pharma, Furtura Medical, Grünenthal, GlaxoSmithKline (GSK), Horizon Pharma, Lundbeck, Menarini, MSD, Pfizer, Reckitt Benckiser, Sanofi Aventis, Urgo, Astellas, and Vifor Pharma.

MPL has received honoraria for consultation from Baxter Pharmaceuticals, CSL Behring, and LfB, and he has received a travel support grant from Grifols. He has no interests to declare related to this review.

## SOURCES OF SUPPORT

### Internal sources

- Oxford Pain Relief Trust, UK.

  General institutional support

### External sources

- No sources of support supplied

## NOTES

A restricted search in February 2016 did not identify any potentially relevant studies likely to change the conclusions. Therefore, this review has now been stabilised following discussion with the authors and editors. The review will be re-assessed for updating in four years. If appropriate, we will update the review before this date if new evidence likely to change the conclusions is published, or if standards change substantially which necessitate major revisions.

## INDEX TERMS

### Medical Subject Headings (MeSH)

Diabetic Neuropathies [*drug therapy]; Fibromyalgia [*drug therapy]; Fructose [adverse effects] [*analogs & derivatives] [therapeutic use]; Neuralgia [*drug therapy]; Neuroprotective Agents [adverse effects] [*therapeutic use]; Randomized Controlled Trials as Topic; Topiramate

### MeSH check words

Adult; Humans